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The relationship between *Helicobacter pylori* infection and reflux esophagitis and the long-term effects of eradication of *Helicobacter pylori* on reflux esophagitis

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Abstract

Introduction: Whether the incidence of reflux esophagitis (RE) increases after the eradication of *Helicobacter pylori* (*H. pylori*) is controversial. Few reports have evaluated the presence or absence of RE after a long period of time, taking into account the degree of atrophy and/or administration of acid secretion inhibitors. We investigated the relationship between *H. pylori* and RE taking into account these factors.

Methods: This was a retrospective cohort study with approval by the Ethics Committee. Patients who succeeded in *H. pylori* eradication treatment, and in whom there were images of the gastroesophageal junction on endoscopic examinations within 1 year before eradication treatment and more than 3 years after eradication were included. The degrees of RE and atrophy were retrospectively determined from the endoscopic images. The prevalence of RE before and after eradication and the incidence of newly developed RE after eradication between patients with or without atrophy improvement were compared using Fisher's exact test.

Results: A total of 185 cases (male:female = 104:81; mean age, 63.5 years; mean observation period, 6.4 years) were examined. The prevalence of RE before and after eradication was 1.6% (3/185) and 7.0% (13/185), respectively ($P=0.019$). RE was present in 8 (7.5%) of 106 cases with closed-type atrophy and in 5 (6.3%) of 79 cases with open-type atrophy after eradication ($P=0.75$). Atrophy improved after eradication in 56 cases, of whom 4 (7.1%) had new onset of RE; the degree of atrophy did not improve in 126 cases, of whom 7 (5.4%) had new onset of RE ($P=0.74$). There was no difference between the percentage of cases who took acid secretion inhibitors before and after eradication ($P=0.14$).

Conclusion: The prevalence of RE increased a long time after eradication, even in patients who were taking an acid secretion inhibitor. The prevalence of RE was not related to the degree of atrophy or change in atrophy.

Keywords: eradication, *Helicobacter pylori*, reflux esophagitis

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Introduction

Reflux esophagitis (RE) is one of the most common upper gastrointestinal disorders worldwide.[1,2] The prevalence of RE in Japan is less than that in Europe and the United States, but it has been increasing in Japan in recent years.[3] Various factors such as westernization of the diet and obesity are thought to have contributed to the increase, and the decrease in the number of people infected with *Helicobacter pylori* (*H. pylori*) is also associated with the increase in prevalence of RE.[4] *H. pylori* infection causes chronic active

gastritis in the stomach,[5,6] and infiltrated inflammatory cells secrete inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α, resulting in direct suppression of gastric acid secretion.[7,8] In addition, the long-term presence of *H. pylori* in the fundic gland region causes fundic gland atrophy and reduces gastric acid secretion.[9,10] The gastric acid secretion capacity of *H. pylori*-infected persons is often lower than that of uninfected persons, and the *H. pylori* infection rate is said to be inversely correlated with the prevalence of RE.[11–14] Eradication treatment of *H. pylori* results in elimination of inflammatory cell infiltration and may lead to improvement of atrophy.[6] It has been reported that elimination of inflammation and improvement of atrophy restore gastric acid secretion.[15,16] On the contrary, when *H. pylori* is present in the antrum, greater acid output is often caused; after eradication, acid output decreases and becomes normal.[17,18] The ammonia produced by *H. pylori* acts as a powerful acid neutralizer in the esophagus and disappears after eradication.[19]

Some studies reported that the incidence of RE increases while other studies reported that it does not change after *H. pylori* eradication.[20] Most of these reports evaluated the presence or absence of RE 1 to 2 years after eradication, and few reports evaluated it a long period of time after eradication.[21] Although gastric acid secretion capacity is expected to differ depending on the degree of atrophy, few reports have investigated whether the degree of atrophy is related to the incidence of RE after *H. pylori* eradication.[22] In patients who are infected with *H. pylori*, gastric acid secretion inhibitors are often administered to prevent gastric ulcer and/or duodenal ulcer formation.[23] In many cases, these drugs continue to be administered even after *H. pylori* has been eradicated. The onset of RE is also affected by the use of such acid secretion inhibitors. However, few reports have investigated the prevalence of RE after eradication of *H. pylori* in patients who are or are not taking a proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H2RA).[22]

We investigated the relationship between *H. pylori* infection and RE by investigating the prevalence of RE before *H. pylori* eradication and the prevalence of RE 3 years or more after *H. pylori* eradication, considering the effects of the degree of atrophy and the use of acid secretion inhibitors.

Methods

Study design

This study was a retrospective cohort study. The protocol used for this study was reviewed and approved by the Juntendo University Ethics Committee (20-050). The reporting of this study conforms to the STROBE statement.[24]

Subjects

Patients who underwent *H. pylori* eradication treatment in our department between 2008 and 2013 and in whom *H. pylori* was successfully eradicated were enrolled in this study. A ^{13}C-urea breath test result of 2.5‰ or less (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), or negative result on the stool *H. pylori* antigen test 6 weeks after the end of eradication treatment (SRL, Inc., Tokyo, Japan) was considered as successful eradication of *H. pylori*. Inclusion criteria were the following: patients who underwent endoscopy within 1 year before the start of eradication treatment and had images of the gastroesophageal junction that could be used to determine the presence or absence of RE, and who underwent endoscopy 3 years or more than 3 years after eradication treatment and had the same images as those described above. Patients who had undergone gastrectomy other than endoscopic mucosal resection or endoscopic submucosal dissection were excluded.

Endoscopic findings

Endoscopic images that had been taken by white light endoscopy and image-enhanced endoscopy, if any, were retrospectively viewed, and the presence and degree of RE, the presence and the degree of atrophy, the presence of a gastric and/or duodenal ulcer including ulcer scar, and the presence of esophageal hiatal hernia were determined. The LA-A classification was used to determine the degree of RE.[25] Atrophy was defined as the presence of discoloration of the mucosa, a visible capillary network, low niveau, and fold disappearance in the corpus area.[26,27] The degree of atrophy was evaluated by the Kimura-Takemoto classification, and classified into two types based on the location of the endoscopic atrophic border which was endoscopically recognized by discriminating differences in color and height of the gastric mucosa: closed type (C-1, C-2, and C-3) and open type (O-1, O-2, and O-3).[28] No atrophy was set as C-0 and was

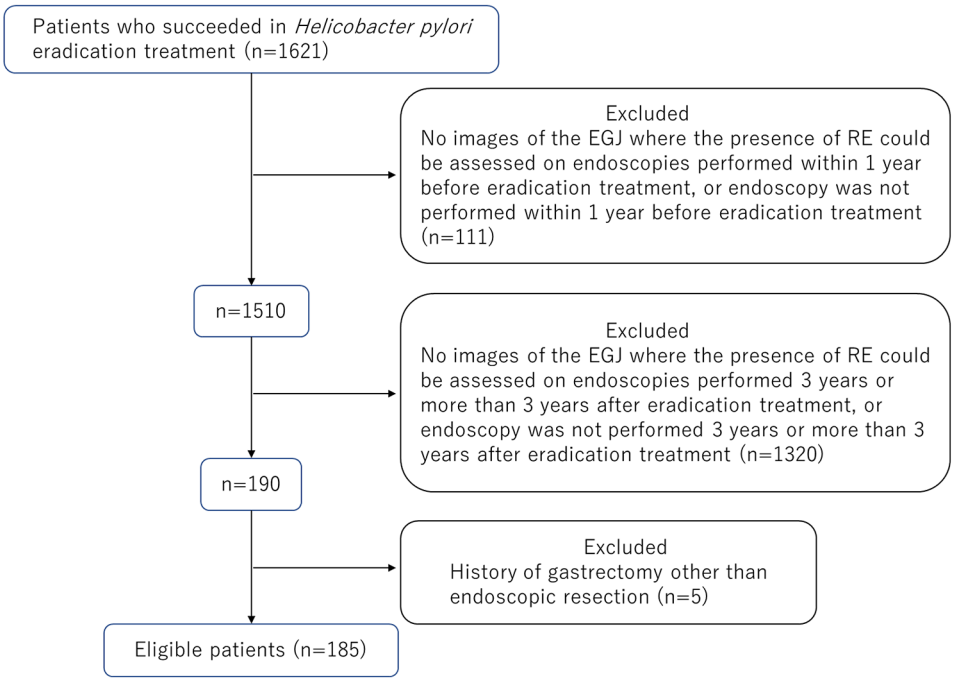

Figure 1. The flow chart of study participants. Some patients who had undergone endoscopy at a different clinic and found to be infected with *H. pylori*, were referred to our department for only *H. pylori* eradication treatment.
GEJ, gastroesophageal junction; RE, reflux esophagitis.

included in the closed-type group. If the degree of atrophy decreased by one grade or more, it was judged that the atrophy was improved. A distance of 2 cm or greater between the lower margin of the palisade vessels and the hiatus of diaphragm was considered to indicate the presence of esophageal hiatal hernia. Among the images of the gastroesophageal junction and esophagus where the presence or absence of RE could be determined, we selected the images obtained during the endoscopic examination at the time closest to and prior to the eradication treatment, and the images obtained during the endoscopic examination with the longest post-eradication time at the time of the search on 28 February 2019. These endoscopic images that had been obtained at the two time points before and after eradication were examined for determination of the presence or absence of RE, atrophy, and esophageal hiatal hernia. The endoscopic images were judged independently by two experienced endoscopists who were board-certified by the Japan Gastroenterological Endoscopy Society (MH and TT), and when the judgments differed, the judgments were unified by discussion. The judgments of the two endoscopists were consistent except for the judgments of the images of four patients.

Acid secretion inhibitors

The presence or absence of administration of acid secretion inhibitors such as PPIs including a potassium-competitive acid blocker, vonoprazan, and H2RAs at the time of endoscopy was investigated in the medical records.

Statistical analysis

Analyses were performed with BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). The prevalences of RE between two groups were compared using Fisher's exact test. The percentages of patients with administration of acid secretion inhibitors before and after eradication were compared using Fisher's exact test. *P* values of less than 0.05 were considered to be statistically significant.

Results

Between 2008 and 2013, 1621 patients underwent successful *H. pylori* eradication, and 1436 patients were excluded according to the inclusion and exclusion criteria. A total of 185 patients were finally included in the analyses (Figure 1). The characteristics of the 185 patients in this

Table 1. Baseline characteristics of the patients who underwent successful *H. pylori* eradication and their observation period.

Cases (n)	185
Gender (male/female (n))	104/81
Age at the time of endoscopy before *H. pylori* eradication whose images were examined in this study (mean ± SD (years))	63.5 ± 9.6
RE before eradication of *H. pylori* (LA-A/LA-B/LA-C/LA-D (n))	2/1/0/0
Atrophy[a] before eradication of *H. pylori* (closed type/open type (n))	81/104
Ulcer including scar before eradication of *H. pylori* (gastric ulcer/duodenal ulcer (n))	24/50
HH before eradication of *H. pylori* (n)	23
Observation period[b] (mean ± SD (years))	6.4 ± 1.9

HH, hiatal hernia; *H. pylori, Helicobacter pylori*; LA, Los Angeles classification; n, number of patients; RE, reflux esophagitis; SD, standard deviation.
[a]Gastric mucosal atrophy was evaluated according to the Kimura–Takemoto classification and was classified by degree into two grades of closed type and open type. No atrophy (n = 4) was included as the closed type.
[b]Observation period, the interval between the two endoscopic examinations before and after *H. pylori* eradication whose images were examined in this study.

study and their observation period, which was defined as the interval between the two endoscopic examinations before and after *H. pylori* eradication whose images we examined in each patient, are summarized in Table 1. The male-to-female ratio was 104:81, and their age at the time of endoscopy before *H. pylori* eradication whose images were examined in this study was 63.5 ± 9.6 years (mean ± standard deviation (SD)). Before *H. pylori* eradication, three patients had RE (two patients with LA-A and one patient with LA-B). Before eradication, there were 77 patients with closed-type atrophy, 104 patients with open-type atrophy, and four patients without atrophy. Twenty-three patients had esophageal hiatal hernia. Twenty-four patients had a gastric ulcer including ulcer scar, and 50 patients had a duodenal ulcer. The mean observation period of the 185 patients was 6.4 ± 1.9 (SD) years.

The prevalence of RE before *H. pylori* eradication was 1.6% (3/185 cases), and the prevalence of RE after eradication was 7.0% (13/185 cases), showing a significant increase ($P = 0.019$). Before eradication, there were two patients with LA-A and one patient with LA-B, as mentioned above, and after eradication, there were seven patients with LA-A and six patients with LA-B; all cases of RE before and after eradication were mild esophagitis (Figure 2). Among the two patients with LA-A esophagitis before eradication, RE disappeared after eradication in one patient and LA-A esophagitis was observed after eradication in the other patient. The patient with LA-B esophagitis before eradication showed LA-B esophagitis even after eradication. Among the three patients with pre-eradication esophagitis, two patients had closed-type atrophy, and one patient had open-type atrophy. Among the 13 patients with esophagitis after eradication, 5 patients had closed-type atrophy and 8 patients had open-type atrophy before eradication. One (33%) of the three patients who had esophagitis before eradication was taking a PPI, and six (46%) of the 13 patients who had esophagitis after eradication were taking a PPI (Table 2).

RE was present in 8 (7.5%) of the 106 cases with closed-type atrophy after eradication and in 5 (6.3%) of the 79 cases with open-type atrophy after eradication ($P = 1.00$) (Figure 3). Among the 182 patients who did not have RE before *H. pylori* eradication, atrophy improved between before and after eradication in 56 patients and atrophy did not improve in 126 patients. Four (7.1%) of the 56 patients with atrophy improvement had new onset of RE after eradication, as did 7 (5.4%) of the 126 patients without atrophy improvement (Figure 4). There was no significant difference in the prevalence rate of newly developed RE between patients with atrophy improvement and patients without atrophy improvement ($P = 0.74$).

After eradication, RE was present in 2 (8.3%) of the 24 cases with gastric ulcer before eradication and in 11 (6.8%) of the 161 cases without gastric ulcer before eradication, showing no significant difference ($P = 0.68$). RE was present in 5 (10%) of the 50 cases with duodenal ulcer before eradication and in 8 (5.9%) of the 135 cases without duodenal ulcer before eradication, also showing no significant difference ($P = 0.34$).

Sixty-seven patients (PPI 42 patients, H2RA 25 patients) were taking acid secretion inhibitors before eradication, and 81 patients (PPI 75 patients, H2RA 6 patients) were taking acid secretion inhibitors after eradication. The percentage of patients who were taking an acid secretion inhibitor before and after eradication was

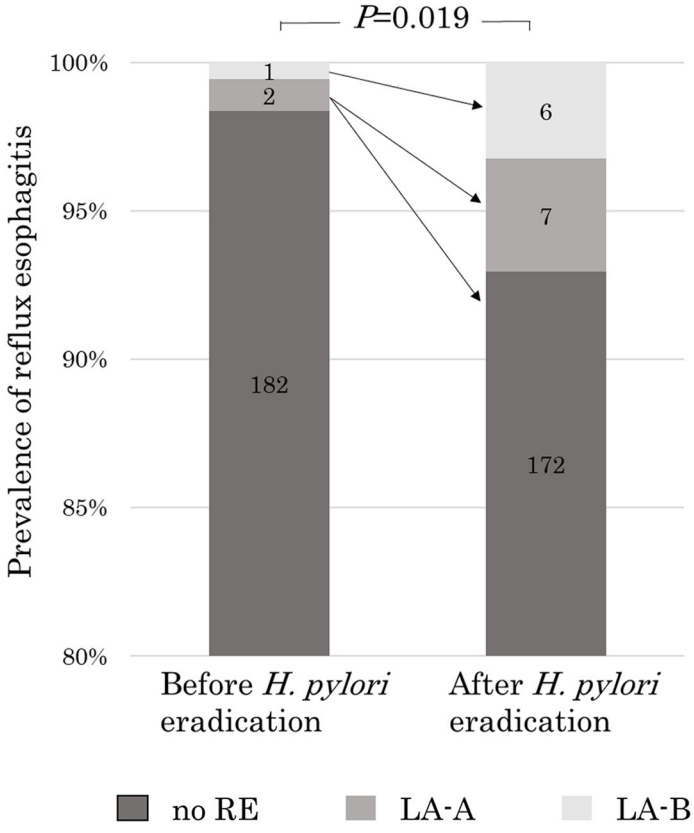

Figure 2. Prevalence of reflux esophagitis before and after eradication of *Helicobacter pylori*. The prevalence of reflux esophagitis was significantly higher after *H. pylori* eradication than before eradication (7.0% (13/185) *vs* 1.6% (3/185), $P=0.019$).
LA, Los Angeles classification; RE, reflux esophagitis.

36.2% (67/185) and 43.8% (81/185), respectively, showing no significant difference ($P=0.14$) (Figure 5).

Discussion

Our study showed that the prevalence of RE significantly increased after *H. pylori* eradication even if some of the subjects were taking acid secretion inhibitors. Moreover, our study showed that the prevalence of RE may not depend on the degree of atrophy.

Many studies have evaluated the prevalence of esophagitis after eradication during a relatively short follow-up period of 1–2 years after eradication, but there are few reports in which patients were evaluated over a long period of time after eradication.[20,21] We evaluated patients before and after a long period of 3 years or more after *H. pylori* eradication. As a result, we found that the prevalence of RE of 1.6% before eradication increased to 7% 3 years or more after eradication. The prevalence of RE in the Japanese adult population is reported to be about 10%.[29] It may be more appropriate to consider that the prevalence of RE after eradication in our study is closer to the prevalence of RE in the general population than to think that its prevalence increased after eradication.

The *H. pylori* infection rate is inversely correlated with the prevalence of RE because inflammatory cytokines suppress gastric acid secretion and because of fundic gland atrophy.[7–10] After eradication, polymorphonuclear neutrophil activity and chronic inflammation improve, and atrophy may also improve.[6,30,31] It has been reported that elimination of inflammation and improvement of atrophy restore gastric acid secretion.[15,16] Therefore, it is expected that the degree of atrophy and changes in atrophy after eradication

Table 2. Characteristics of the patients with reflux esophagitis before and/or after *H. pylori* eradication.

Degree of RE before eradication	Degree of atrophy[a] before eradication	Use of acid secretion inhibitors before eradication	Degree of RE after eradication	Degree of atrophy after eradication	Use of acid secretion inhibitor after eradication	Hiatal hernia	Observation period[b] (years)
LA-A	C-2	–	–	C-2	–	–	6.7
LA-A	O-3	PPI	LA-A	C-1	PPI	+	8.3
LA-B	C-1	–	LA-B	C-1	PPI	+	3.8
–	O-2	–	LA-B	O-1	PPI	–	9.7
–	O-1	PPI	LA-B	C-2	PPI	–	3.1
–	C-2	–	LA-B	C-1	PPI	+	7.3
–	O-2	–	LA-A	C-1	–	–	10.5
–	O-3	–	LA-A	O-3	–	–	5.8
–	O-3	–	LA-A	O-3	–	–	3.6
–	O-3	–	LA-A	O-3	–	–	5.7
–	O-2	PPI	LA-B	O-2	–	–	4.9
–	C-2	–	LA-A	C-2	PPI	–	9.3
–	C-2	–	LA-A	C-2	–	–	7.9
–	C-1	–	LA-B	C-1	–	–	5.8

H. pylori, Helicobacter pylori; LA, Los Angeles classification; PPI, proton pump inhibitor; RE, reflux esophagitis.
[a]Gastric mucosal atrophy was evaluated according to the Kimura–Takemoto classification and was classified by degree into two grades of open type (O) and closed type (C).
[b]Observation period, the interval between the two endoscopic examinations before and after *H. pylori* eradication whose images were examined in this study.

affect the prevalence of RE.[32] However, in this study, no associations were found between the degree of atrophy or the degree of change in atrophy after eradication and the prevalence of RE. It was considered that factors other than gastric acid secretion were involved in the development of RE. Ammonia produced by *H. pylori* acts protectively against RE and eradication may eliminate the protective effect and cause esophagitis.[19,22] Kyphosis and hernia may occur over the long term after eradication.[33] Patients' body mass index sometimes increases after eradication.[34,35] Therefore, these factors might be involved in the development of RE after eradication. The prevalence of esophagitis is affected by acid secretion inhibitors. In this study, there was no difference in the proportion of patients taking acid secretion inhibitors before and after eradication.

One limitation of this study is that the optimal sample size was not calculated. This study was a retrospective study, and the number of cases could not be increased. Therefore, since the prevalence of RE and the incidence of newly developed esophagitis were low, there may be β-errors among the items that were judged to be not significantly different. Also, in this study, endoscopic atrophy was not confirmed by histological examination. However, it has been reported that there was a strong correlation between endoscopic diagnosis of gastric atrophy according to the Kimura–Takemoto classification and histological diagnosis of gastric atrophy.[27,36] Moreover, because of the retrospective nature of this study, the medication history may be inaccurate. Information on body mass index and symptoms was unknown and could not be considered. Since

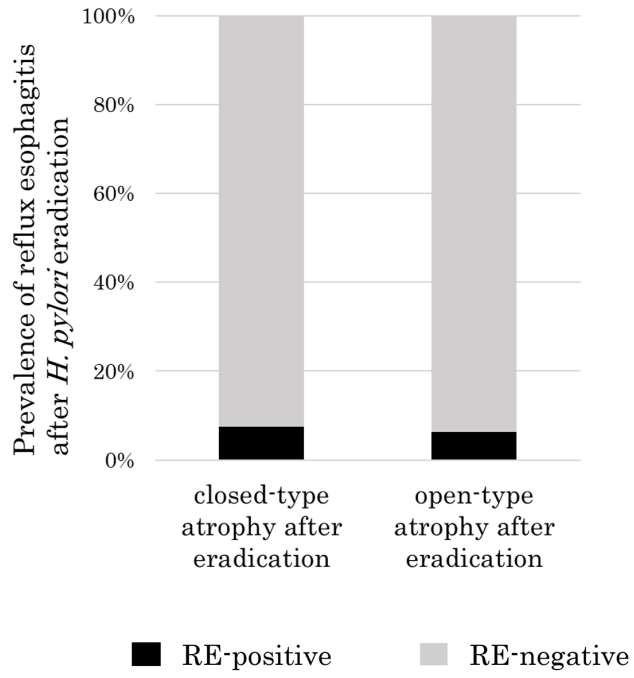

Figure 3. Prevalence of reflux esophagitis after eradication in patients with the closed-type or open-type atrophy after eradication of *Helicobacter pylori*. There was no significant difference in the prevalence of reflux esophagitis after *H. pylori* eradication between patients with closed-type atrophy and those with open-type atrophy after eradication (7.5% (8/106) *vs* 6.3% (5/79), $P = 1.00$).
RE, reflux esophagitis.

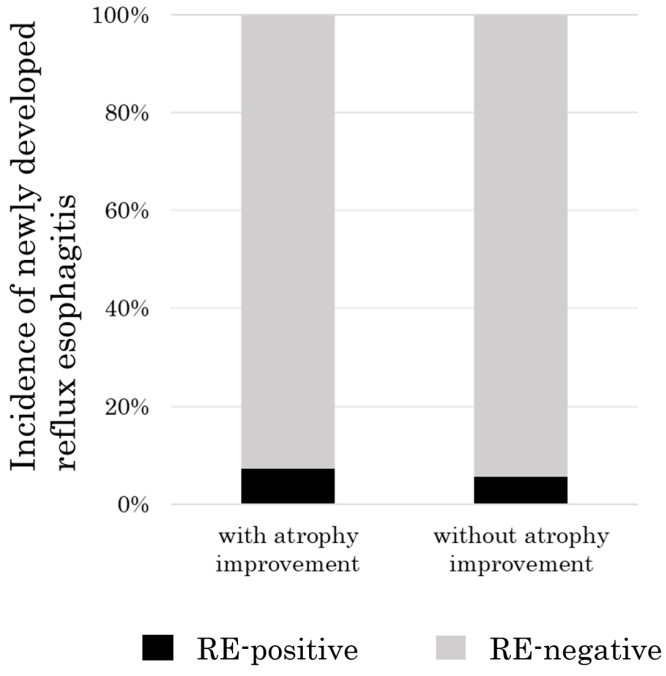

Figure 4. Incidence rate of newly developed reflux esophagitis after *Helicobacter pylori* eradication between patients with or without improvement of atrophy. The three patients with reflux esophagitis before *H. pylori* eradication were excluded from this analysis. There was no significant difference in the incidence of newly developed reflux esophagitis after eradication between patients with or without atrophy improvement (7.1% (4/56) *vs* 5.4% (7/126), $P = 0.74$).
RE, reflux esophagitis.

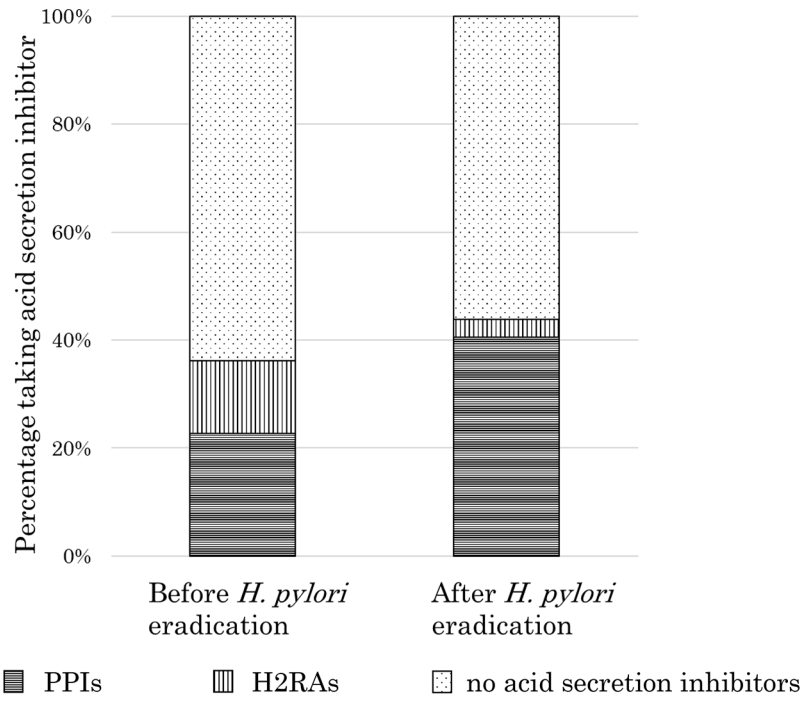

Figure 5. Comparison of the percentage of patients who were taking acid secretion inhibitors before and after eradication of *Helicobacter pylori*. There was no significant difference in the percentage of patients who were taking acid secretion inhibitors before and after eradication of *H. pylori* (36.2% (67/185) *vs* 43.8% (81/185), $P = 0.14$).
H2RA, histamine H2-receptor antagonist; PPI, proton pump inhibitor.

no patient had undergone measurement of gastric pH, it was not possible to know how much gastric acid was actually secreted.

In this study, it was shown that the prevalence of RE increased a long period of time after *H. pylori* eradication, even among subjects who were taking acid secretion inhibitors. The prevalence of RE after eradication and incidence of new onset of RE after eradication were not related to the degree of atrophy or changes in atrophy.

In the future, it is necessary to investigate factors related to the occurrence of RE other than atrophy and to examine changes in gastroesophageal reflux symptoms before and after eradication of *H. pylori* over a long period of time.

Author contributions

MH and AN designed the study. MH, KU YA, HU, YS, and DA acquired data. MH and TT judged endoscopic images. MH analyzed and interpreted the data, and drafted and revised the manuscript. All authors reviewed the manuscript and approved the final version of the manuscript.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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